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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,991	09/16/2003	Leonard F. Bjeldanes	B03-074-1	4613

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RICHARD ARON OSMAN
4070 CALLE ISABELLA
SAN CLEMENTE, CA 92672

EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
02/11/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

RICHARD@SCI-TECH.COM
jan@sci-tech.com

Office Action Summary	Application No.	Applicant(s)	
	10/664,991	BJELDANES ET AL.	
	Examiner	Art Unit	
	Timothy E. Betton	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *8-14 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Remarks and Declaration filed 8 September 2007 have been acknowledged and duly made of record.

Applicants' argue the properness drawn to alleged lack of applicable prior art by Nachschon-Kedmi reference. Further applicants' argue the relevance of the Safe et al, the secondary reference.

In view of said arguments made by applicants', the Remarks have been considered but are not found persuasive.

The applicants' provide no evidence of a filing date which pre-dates the Nachschon-Kedmi reference. Applicant's filing date is officially recorded as 16 September 2003. The Nachschon-Kedmi reference is cited as June 2003 publication, which is sufficiently postdated by applicant's filing date.

Secondly, The Safe et al. reference teaches similar subject matter in relation to claimed invention as only in the alternative a general DIM administration to inhibit the proliferation of androgen-independent cells. The skilled artisan would instantly be inclined to recognize that applicants' alleged discovery of finding that DIM is a potent antiandrogen would be quite identical to Safe's disclosure which teaches DIM can inhibit the proliferation of androgen-independent cells.

The declaration filed on 1 May 2007 under 37 CFR 1.131 has been considered but is ineffective to overcome the Nachschon-Kedmi reference.

The evidence submitted is insufficient to establish diligence from a date prior to the date of reduction to practice of the Nachschon-Kedmi reference to either a constructive reduction to practice or an actual reduction to practice. The evidence is not commensurate in scope with the claims without an explanation supporting such findings is unacceptable.

Evidence of fact is supported in the instance that one of the named inventors is indicated as the leading author of the publication as disclosed in the instant declaration. However, evidence of fact is absent in regard to comparative test results, correlative data, synthetic representation of possession of the invention, etc. Accordingly, the mere disclosure that the secondary reference teaches no more than the inventors prior publications is erroneous in view of prevailing evidence that an appropriate filing date is the requirement for possession of an invention.

Thus, applicants' statement drawn to preparing, reviewing, and revising is unsupported and there are no explanations or conclusory statements supported by factual evidence (3rd paragraph).

Specifically, applicants' purport in the instant declaration that the said applicants' were in possession of the claimed subject matter between the March 27, 2003 to September 16, 2003. Substantive evidence supporting applicants' allegations of preparing, reviewing, revising, with the exception of filing is absent in the instant declaration, specifications and current claims. The embodiments contained within the instant declaration are drawn primarily to the chemical compound DIM which appears to differ in the inventive objective of what the scope of the instant claims intends.

For the reasons given above in response to applicants' Remarks, the 103(a) rejection is maintained.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant invention.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vitamin Research Products (VRP Staff, DIM Acts as a Potent Anti-Androgen, J Biol Chem, (2003 March 27), printed pages 1 and 2, especially page 1) and Nachshon-Kedmi et al. in view of Safe (PGPUB 2002/0115708 A1).

Nachshon-Kedmi et al. teach a cell-line study directed toward the apoptotic effects of 13C and DIM on prostate cancer cells (Abstract, page 747, 1st column).

Distinct biochemical and morphological features, including cell shrinkage, characterize the apoptotic process. Cell shrinkage is a physiological occurrence, which, to the ordinary,

skilled artisan would constitute a form of reduction as antiandrogenic response (page 750, column 2, lines 6-10).

VRP Staff teach DeIndole-3-carbinol (I3C), which the body converts into Diindolylmethane (DIM), is found in cruciferous vegetables such as broccoli, brussel sprouts and cauliflower. DIM and I3C alter the way the body metabolizes estrogen, from the cancer-causing pathway to the cancer-inhibiting pathway. Researchers have now unveiled evidence that DIM also affects testosterone. While the prostate needs testosterone to function normally, it is also thought to play a role in the early stages of prostate cancer and physicians typically treat prostate cancer patients with anti-androgen drugs.

In two papers published in the Journal of Biological Chemistry, researchers report that DIM significantly halted proliferation of androgen-dependent human prostate cancer cells. In one of the studies, androgen-dependent prostate cancer cells treated with DIM grew 70% less than androgen-dependent untreated cells. DIM also inhibited dihydrotestosterone (DHT) stimulation of DNA synthesis in the androgen-dependent cancer cells. These effects were not seen in androgen-independent prostate cancer cells.

To determine whether men are at risk for prostate cancer, they are usually tested for levels of prostate-specific antigen (PSA), a growth factor for prostate cancer. In prostate cancer cells, DIM reduced intracellular and secreted PSA protein levels caused by DHT.

The researchers determined that DIM's molecular structure is similar to Casodex, a synthetic anti-androgen drug. (page 1 of 2).

Nachshon-Kedmi et al. teach prostate hyperplasia cell lines with variable differences in p53 status (page 746). The p53 gene is significantly involved in the regulative aspect of the apoptotic process (page 752, column 1, last paragraph)

Additionally, said reference makes the claimed invention obvious via the explanation of Western blot analysis, i.e., the determining, contacting, and reducing method steps of claimed invention (page 747).Further, said reference teaches the actual process by which apoptosis occurs. Principally, during apoptosis, PARP is cleaved from its precursor having a mass of 116kDa, to yield an 85-kDa fragment. There is cleavage in PARP in all cell lines, but to varying degrees. The skilled artisan would at once recognize the reduction of cellular matter via the marked mass decrease from 116kDa to 85kDa.

Safe teaches methods and compositions for the treatment of a wide array of cancers and tumors. In illustrative embodiments, diindolylmethanes, C-substituted diindolylmethanes, and analogs thereof have been described, which when administered either alone, or in combination with other anti-cancer or anti-tumorigenic compounds, provide new therapies for the treatment of prostate cancer (Abstract, [0050], last line of instant paragraph).

Safe teaches a practicing administration (in vitro and in vivo) to human patients in need thereof via inhibition of prostate cancer cell growth [0065, 0049].

Safe discloses the directed use of DIM and derivatives thereof for the specific contacting, detecting, and inhibiting via a gel mobility shift assay for prostate cancer cells (Brief

description of Drawings – Table CWU – DRTL (1)) in a comparative study to estrogen-dependent pathologies. Safe further discloses the practicing methods of administering said antiandrogenic agent in claims 16, 34, 51, and 69, therein.

Safe teaches derivatives of the practicing DIM core structure that are also taught in the instant application. In said referenced publication on page 3, section [0039] under the heading: Definitions, said structure is disclosed. Derivatives of the core structure are disclosed in the instant application on page 3 of the specification under the heading: Summary of Invention. Safe discloses in published claims, the *in vitro* method (by use of assays which are disclosed empirical series of method steps used to detect a reaction) of treating cancer, the method comprising obtaining a mammal comprising cancer cells, and administering to the mammal a composition comprising an effective dose of a compound of the said formula. Claims 17-19 are made obvious over claims 16, 34, 51, and 69 in Safe obvious over using this related core structure in the use of treatment against the specific cancer-types, i.e., prostate cancer and pathologies thereof.

Safe teaches detection on page 5, Example 2, section [0058] in that a process is disclosed where inhibition was determined, i.e., where clear proliferation of cancer cell lines were significantly inhibited. Further, detection is implied in said reference where sensitive cells were noticeably inhibited at the lowest concentration.

Safe, in accordance, more specifically teaches detection on page 4, section [0047] of said referenced publication where resolution of the mixture using chiral chromatography column would result in the isolation of purified or pure enantiomers products. Furthermore, Safe teaches the use of thin-layer chromatography and liquid chromatography in section [0067] (page 6), both well-established detection methods and/or detection facilitators.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine together the teachings and methods of Nachshon-Kedmi et al. and Safe. The VRP Staff reference, however, provides the most encompassing reasoning and disclosure in relation to claimed invention to combine the other two references, N-Kedmi et al. and Safe. VRP Staff teach the central inventive objective of claimed invention. The skilled artisan would have at once recognized the reasonable expectation of success if the teachings and methods of Nachshon-Kedmi et al. and Safe were incorporated together with the teachings and methods of VRP staff. Safe suggests and supports the motivation to combine via the disclosure of particular limitations, which make the instant set of claims obvious. Likewise, the motivation to combine all references as mentioned would have been obvious and proper to one of ordinary skill due to overlap of core compounds, assaying methods, and goal of regimen.

It is well known in the art that I3C and DIM (a predominant conversion product of I3C) is a potent antiandrogenic based on the VRP reference. Therefore, It would have been *prima facie* obvious to combine that, which is taught in Nachshon-Kedmi et al. with that which is taught by Safe to result in the practice of the limitations of claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

SHENGJUN WANG
PRIMARY EXAMINER

Licensing Officer	UNIVERSITY OF CALIFORNIA, BERKELEY OFFICE OF TECHNOLOGY LICENSING **DISCLOSURE AND RECORD OF INVENTION FORM** (please read instructions and complete all pages)	B03-074 Case Number
Date Assigned		Class Code

Note: When completed, the Disclosure and Record of Invention Form is an important legal document. Care should be taken in its preparation. Please refer to accompanying instructions. If you need assistance, call the Office of Technology Licensing (UC Berkeley Patent Office) at (510) 643-7201. Information contained in this document is maintained in confidence by the the Office of Technology Licensing and normally will not be released to others except with attorney-client privilege, to research sponsors as required by contract, or under appropriate secrecy agreements, until a patent application is filed, the information is published, a determination not to file a patent application is made, or as may be required by law. The information contained should not be disclosed to others outside the University, except as described in section 4(f.), without the approval of the Office of Technology Licensing.

1. Title of Invention:

Indole-3-carbinol and 3,3'-diindolymethane, and derivatives, as antiandrogenic and prostate cancer therapeutic and protective agents.

2. A. Brief Summary of Invention (include novel features and advantages. Use additional sheets if necessary.)

Indole-3-carbinol (I3C) and its derivative, 3,3'-diindolylmethane (DIM), are natural compounds present in cruciferous vegetables. Our continuing studies of the cancer protective effects of these substances have shown that I3C and DIM inhibit the proliferation of androgen sensitive prostate tumor cells by different mechanisms. I3C blocks cell proliferation by a process that involves the selective inhibition of expression of cyclin-dependent kinase 6 (CDK6) protein and transcripts, and stimulated production of the p16 CDK inhibitor protein. DIM, however, can affect prostate tumor cell growth by at least two mechanisms. We have shown that DIM can bind to and block the activity of the androgen receptor (AR), and that DIM can activate the estrogen receptor (ER) by a process that does not involve binding to the receptor. There is considerable evidence in the literature that the combination of AR inhibition and ER activation is of crucial importance in the control of prostate tumorigenesis. Thus, DIM is the first example of a substance that is both a pure AR antagonist and an ER agonist. Because of their multiple antiproliferative mechanisms, the use of I3C and DIM, and more active derivatives, hold great promise for the control of prostate cancer.

B. Detailed Description of Invention (attach additional single-sided sheets)

Identify any references, patent applications, or other publications of which you are aware and which you believe to be pertinent to this invention. Please attach a copy of each of these references, if available.

(see attachment)

3. A. Funding Source/Sponsor | Contract/Grant No.(s) | Principal Investigator

(NOTE: IT IS EXTREMELY IMPORTANT THAT THIS SECTION IS COMPLETED)

see under disclosure chem lit. -Beni

~~California Cancer Research Project — sc#09147V-10010 — PI - L.F. Bjeldanes~~

~~National Institute of Environmental Health Sciences Center — Grant P30-ES01896 — PI - L.F. Bjeldanes~~

B. This invention utilized data or materials from (check as many as apply):

( ) Celera's proprietary database
( ) Affymetrix chips
( ) A Material Transfer Agreement – "MTA" – (non-UC material)
( ) Other proprietary sources: specify_____.

4. Events For subject invention, what was the:	Date	Comments/References
a. Date of first conception of idea	May 1999	
b. Date of first description of complete invention, oral or written conception: identify document, page numbers and location of document	March 2003	
c. Date of first successful demonstration of reduction to practice of invention	Not yet used in practice	
d. Date of first publication containing full description of invention (very important – establishes bar date)	DIM publication in press in JBC – on-line 4/1/03 I3C publication in preparation	
e. Dates of external oral disclosures to non-UC employees		
f. Date of planned submission of report, paper, thesis describing invention		

5. If any proprietary material (e.g., cel. e, antibody, plasmid, computer software, hemical compound) obtained from outside your laboratory was used to develop this invention under a restrictive written or oral transfer agreement (other than a normal purchasing agreement), please attach a copy or summary of that agreement.

6. INVENTOR INFORMATION. Note: Please fill out completely to allow for timely and accurate distribution of royalty income (to add more inventors go to page 3).

Leonard F. Bjeldanes 3/31/03
Signature Date

Leonard F. Bjeldanes Professor
Print name Title

Nutritional Sciences and Toxicology
Dept./ORU (required for income distribution) (or Employer if not UC)

217 Morgan Hall, #3104
Rm., Bldg., Mail Code (or business address)

lfb@nature.berkeley.edu
e-mail address

Berkeley CA 94720-3104
City State Zip

510-642-1601; 510-642-0862 510-642-0535
Telephone No. (Office/Lab) Fax No.

1407 Stockton Ave. El Cerrito, CA
Home Address

United States of America
Country of Citizenship (required for patenting)

3/31/03
Signature Date

Gary L. Firestone Professor
Print name Title

Molecular and Cell Biology
Dept./ORU (required for income distribution) (or Employer if not UC)

591 A LSA, #3200
Rm., Bldg., Mail Code (or business address)

glfire@uclink4.berkeley.edu
e-mail address

Berkeley CA 94720-3200
City State Zip

510-642-8319; 510-642-3541 510-643-6791
Telephone No. (Office/Lab) Fax No.

Home Address

U.S.A.
Country of Citizenship (required for patenting)

ADD ADDITIONAL INVENTORS ON FOLLOWING PAGES ----------->

7. For any Inventor named (item 6, above) who is not employed full-time by the University of California, please identify other employers (e.g., Veterans Administration, Howard Hughes Medical Institute, USDA), the percent of salary time funded by such other employer, and the nature of the other employment (such as research, teaching or clinical duties).

8. Technically Qualified Witnesses (Two Required) - invention disclosed to and understood by:

3/31/03
Signature Date

JOSEPH L. NAPOLI
Print name

3/31/03
Signature Date

SHARON FLEMING
Print name

Please submit this form with original signatures to:

Director
Office of Technology Licensing
2150 Shattuck Avenue, Suite 510, MC 1620
Berkeley, CA 94720-1620

INVENTOR INFORMATION (CON NUED FROM PAGE 2). Note: Pleas. .ll out completely to allow for timely and accurate distribution of royalty income.

Hien Le	04/07/03
Signature	Date
Hien Le	Ph.D.
Print name	Title
Dept./ORU (required for income distribution) (or Employer if not UC)	
Rm., Bldg., Mail Code (or business address)	
hien_oi@yahoo.com	
e-mail address	
City State Zip	
Telephone No. (Office/Lab) Fax No.	
8916 Libra Drive, San Diego, CA 92126	
Home Address	
U.S.A.	
Country of Citizenship (required for patenting)	

Signature Date	Signature Date
Print name Title	Print name Title
Dept./ORU (required for income distribution) (or Employer if not UC)	Dept./ORU (required for income distribution) (or Employer if not UC)
Rm., Bldg., Mail Code (or business address)	Rm., Bldg., Mail Code (or business address)
e-mail address	e-mail address
City State Zip	City State Zip
Telephone No. (Office/Lab) Fax No.	Telephone No. (Office/Lab) Fax No.
Home Address	Home Address
Country of Citizenship (required for patenting)	Country of Citizenship (required for patenting)